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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,791	CHIEN ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19 and 24-31* is/are pending in the application.

4a) Of the above claim(s) *25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 9/11/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 18-19, 24-31 are pending. Claims 25-31 are withdrawn. Claims 1-17, 20-23, 32-35 are canceled. Claims 18-19, 24 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-19, 24 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are directed to a method for treating a loss of cardiac muscle contractility associated with heart failure comprising: delivering an expression construct to myocytes in a mammalian host suffering from heart failure, wherein the expression construct provides an expressible polynucleotide encoding a phospholamban (PLB) molecule having a single point mutation consisting of S16E, wherein expression of a therapeutic level of the polynucleotide stimulates improved cardiac muscle contractility. Claims 19 and 24 limit the expression construct to a viral vector.

The specification discloses the amino acid sequence of an H6-PLB (S16E mutant)-ANT protein and an H6-PLB (V49A mutant)-ANT protein (SEQ ID: Nos. 18 and 19 respectively) (specification p 31, lines 23-24). However the specification fails to provide guidance for

delivering an expression construct to any and all myocytes by any and all routes of administration in a mammalian host suffering from heart failure, wherein the expression construct provides an expressible polynucleotide encoding S16E, wherein expression of a therapeutic level of the polynucleotide stimulates improved cardiac muscle contractility. The guidance provided by the instant specification fails to correlate the disclosed amino acid sequence of S16E (SEQ ID NO: 18) to the delivery of an expression construct encoding for the S16E mutated PLB (SEQ ID NO: 18) to any and all myocytes in vivo, expressing a therapeutic level of the protein in vivo resulting in treatment of loss of cardiac muscle contractility associated with heart failure. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed method for treating loss of cardiac muscle contractility associated with heart failure. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

As a first issue the instant invention relates to treatment of loss of cardiac muscle contractility associated with heart failure via a method of gene therapy using a construct encoding a phospholamban (PLB) molecule having a single point mutation consisting of S16E to any and all mocytes, in vivo. The specification discloses the protein sequence of the H6-PLB (S16E mutant)-ANT protein (SEQ ID. Nos. 18) (specification p 31, lines 23-24). The specification fails to provide guidance with regard to delivering said construct in vivo to any and all myocytes in vivo.

The art teaches that mutant S16E PLB gene therapy is an unpredictable art with respect to targeting any and all myocytes in vivo, by any and all routes of administration of the S16E PLB, resulting in expression of a therapeutic level of S16E PLB protein in vivo, necessary to provide treatment for loss of cardiac muscle contractility associated with cardiac heart failure.

For example, cardiomyocytes, being post-mitotic and terminally differentiated cells, present their own unique challenges and several methods for myocardial gene delivery each presents its own limitations and benefits (**Thompson et al,** Annals of Medicine, 36(Suppl 1): 106-115, 2004) (p 109). For example, direct myocardial injection is burdened with the delivered gene expressing only in and around the small region of myocardium surrounding the needle tack, or pericardial injection is an effective means of transfection in rats and could be proved useful for minimally invasive human delivery if large animal models show similar results (**Thompson et al,** (p 109). With respect to use of viral vectors for cardiac gene transfer **Thompson** reports several limitations such as short duration of expression, small insert capacity, difficulty in production of high tier stock, low ability to infect non-dividing cells and low efficiency of transfection (p 111, and Table 1).

Barbato et al, (Critical Reviews in Clinical Laboratory Sciences, 40(5): 499-545, 2003) while reviewing the status of the role of gene therapy in the treatment of cardiovascular diseases notes the challenge of gene therapy is the actual delivery of the genetic material into the targeted tissue in sufficient quantities to result in the synthesis of adequate quantities of gene product to elicit the desired therapeutic action while limiting systemic and/or local toxicity (p 501, under vectors). Vectors differ in transfection efficiency, immunogenicity and ability to transduce dividing or quiescent cells (**Barbato et al,** p 501, 2nd paragraph under vectors). For example, the transient nature of transgene expression with adenoviral vectors may limit the use of these vectors to the treatment of acute vascular injury and have less utility in treating chronic or progressive disorders such as heart failure and atherosclerosis (**Barbato et al,** p 504, 2nd paragraph).

Beck et al, (Current Gene Therapy,4: 457-467, 2004) reports the technical challenges related to cardiovascular gene transfer are still significant with respect to (i) efficiency of gene delivery, (ii)

achievement of high and stable level of transgene expression in a specific cell-type and (iii) design and administration tools and vectors that are safe for clinical application (p 463, bridge 1st to 2nd column). Therefore the prior art challenges the underlying assumption that the S16E mutated PLB transgene will be expressed at sufficient therapeutic levels at the targeted myocytes, in vivo, particularly in any and all myocytes in vivo for treating loss of cardiac muscle contractility associated with heart failure. Thus, while progress has been made in recent years for gene transfer in vivo, vector targeting to cardiomyocytes in the heart tissue and any and all myocytes in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art.

As a second issue, the instant invention encompasses the treatment of loss of cardiac muscle contractility associated with heart failure by administering any viral vector encoding the S16E mutant of phospholamban gene. Considering the complexities involved the etiology of loss of cardiac muscle contractility associated with heart failure instant specification fails to provide an enabling disclosure, which establishes the S16E mutant form of phospholamban gene is capable of treating loss of cardiac muscle contractility associated with heart failure. While progress has been made in recent years for in vivo gene transfer, vector targeting in vivo to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that could not have been overcome by routine experimentation. These include, the fate of DNA itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and

the protein being produced (**Ecke et al Goodman & Gilman's** The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101).

For example considering the instant specification it is unclear how one skill in the art would treat loss of cardiac muscle contractility associated with heart failure by administering a S16E mutant phospholamban gene to any and all myocytes in vivo. The RAC advisory panel clearly emphasized the need for a greater understanding of an underlying mechanism that contributes to a disease along with the pathogenesis of the disease. The state of the art at the time of filing was such that the heart failure is almost always a chronic, long-term condition, although it can sometimes develop suddenly. This condition may affect the right side, the left side, or both sides of the heart. The factors that leads to heart failure include family history (congenital heart disease), Ischemic heart disease/Myocardial infarction (coronary artery disease), Heart muscle disease (dilated cardiomyopathy, hypertrophic cardiomyopathy) or inflammation (myocarditis), Arrhythmia, Hypertension, Cardiac fibrosis, Coarctation of the aorta, Aortic stenosis/regurgitation, Mitral regurgitation, Pulmonary stenosis/Pulmonary hypertension/Pulmonary embolism all leading to cor pulmonale and Mitral valve disease, arrhythmia or dysrhythmia (See **Lip et al,** BMJ 320:104-107, 2000). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectation of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519,

536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion")). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. In the instant case, such reasonable detail is lacking. The specification provides no guidance on how to use the compounds of claim 37 as beta-cell growth factors. See Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297 (CA FC 2005) which teaches: "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

In light of the above, the instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of delivering the S16E mutated PLB construct into any and all myocytes in vivo by any and all routes of administration of said construct in vivo resulting in the treatment of loss of cardiac muscle contractility associated with heart failure raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of S16E PLB gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating loss of cardiac muscle contractility associated with hear failure by S16E PLB gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for delivering the S16E construct to any and all myocytes in vivo, by

any and all routes of administration of said construct in vivo, for treatment of loss of cardiac muscle contractility associated with heart failure, the lack of direction or guidance provided by the specification for delivering the S16E construct to any and all myocytes in vivo, by any and all routes of administration of said construct in vivo, for treatment of loss of cardiac muscle contractility associated with heart failure, the absence of working examples that correlate to delivering the S16E construct to any and all myocytes in vivo, by any and all routes of administration of said construct in vivo, for treatment of loss of cardiac muscle contractility associated with heart failure, the unpredictable state of the art with respect to delivering the S16E construct to any and all myocytes in vivo, by any and all routes of administration of said construct in vivo, for treatment of loss of cardiac muscle contractility associated with heart failure, the undeveloped state of the art pertaining to the treatment of loss of cardiac muscle contractility associated with heart failure, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue that the Crystal et al paper is referring to the inventor's post-filing publication of the hamster model associated with the S16E PLB delivery in the heart of BIO14.6 hamsters by stating:

"...persistent activation of SERCA is an obvious therapeutic strategy for heart failure. But how can this be accomplished? In an attempt to meet this challenge, the [inventor] Chien laboratory used a gene therapy approach. They delivered a mutant form of phospholamban to the heart in a vector already shown to be effective at transferring and persistently expressing genes in the heart recombinant adeno-associated virus serotype 2 vector (AAV2). The mutant phospholamban (S16E) has a serine replaced by a glutamate at one of its two phosphorylation sites, mimicking phosphorylation of the serine...
Theoretically, delivering an S16E form of phospholamban to heart cells should increase SERCA2 activity, and thus increase contractility. A variety of in vitro and acute in vivo models suggested that this strategy should work. However, heart failure is a chronic condition, and thus the critical question is whether this approach would persistently prevent heart failure? To address this question, Chien's group used an animal [mammalian] model of progressive cardiomyopathy and heart failure, the BIO 14.6 hamster. With an adeno-associated virus vector,

Chien and his co-workers were able to persistently express S16E phospholamban in the heart. They also showed that S16E phospholamban gene therapy, despite not addressing the primary cardiac abnormality in the BIO14.6 hamsters, [still] enhanced a variety of parameters associated with cardiac function..."

Applicants argue that Crystal referring to inventor's post filing publication of the hamster model results, the Crystal et al paper concluded that these data are sufficient to demonstrate that the invention works as claimed to improve cardiac contractility.

These arguments are not persuasive because the post filling editorial of Crystal in reference to the Applicant's hamster model does not provide guidance for delivering the S16E PLB by way of the claimed methods resulting in the treatment of loss of cardiac muscle contractility associated with heart failure at the time of filing of the instant application. In fact, Crystal notes that it is unpredictable if delivery of the S16E PLB in the heart will result in loss of cardiac muscle contractility by stating: "Theoretically, delivering an S16E form of phospholamban to heart cells should increase SERCA2 activity, and thus increase contractility". As discussed above most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectation of current gene therapy protocols have been over sold without any apparent success.

Applicants further argue that the work in a hamster model of cardiomyopathy referenced by Crystal, et al. is described by the inventors in previously filed, co-pending application Serial No. 09/954,571 (US PG Pub. No. 2002/0032167, filed 9/11/2001). For ease of reference, the pertinent passages of the '571 Application are submitted herewith in Appendix A.

However the applicant's arguments are found not persuasive. The invention as claimed encompasses a method of treating heart failure associated with loss of cardiac muscle contractility, wherein the S16E PLB gene is delivered to any and all myocytes in vivo via any and all means of administration. For example, the invention as claimed encompasses the

administration of the S16E PLB gene via any and all routes of administration (systemic, topical, intra-dermal, oral, nasal and direct injection etc) using any viral or non-viral vector.

As discussed above applicants failed to provide evidence to overcome the unpredictability of delivering the S16E PLB in vivo by way of the claimed methods resulting in a effect in vivo because it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Furthermore, the disclosed amino acid sequence of the S16E PLB gene (SEQ ID NO: 18) is not predictive of in vivo gene delivery to any and all myocytes for gene therapy because of the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials.

Furthermore, treating a heart failure as claimed wherein the S16E PLB gene is delivered via any and all means and to any target site is not considered routine in the art and without sufficient guidance to a specific target site and method of specific vector delivery the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. see in re wands 858 f.2d 731, 8 uspq2nd 1400 (fed. cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. see ex parte Singh, 17 uspq2d 1714 (BPAI 1991). Therefore considering the state of the art and lack of guidance provided in

the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18, 19, 24, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 70, 71, 72, 98, 99, 100, 101 of copending Application No. 09/954571. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims embrace treatment of heart failure in a patient comprising administering to a patient an expression construct encoding a protein having an S16E mutation. The breadth of the scope of the claims recited in the '571 includes is to treatment of heart failure associated with loss of cardiac muscle contractility in a patient comprising administering to cardiac muscle said S16E PLB mutant nucleic acid and obviously encompasses the S16E PLB mutant nucleic acid as embraced in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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